

**UNITED STATES DISTRICT COURT  
NORTHERN DISTRICT OF OHIO**

**EASTERN DIVISION**

**IN RE: NATIONAL PRESCRIPTION  
OPIATE LITIGATION**

THIS DOCUMENT RELATES TO:

*The County of Summit, Ohio, et al. v.  
Purdue Pharma L.P., et al.,*  
Case No. 18-op-45090

*The County of Cuyahoga, Ohio, et al. v.  
Purdue Pharma L.P., et al.,*  
Case No. 17-op-45004

MDL No. 2804

Case No. 1:17-md-2804

Judge Dan Aaron Polster

**Defendants' Reply in Support of Their Motion to Exclude  
Expert Testimony of Katherine Keyes, Anna Lembke & Jonathan Gruber  
Re The "Gateway Hypothesis" of Causation**

Defendants moved to exclude the opinions of three of Plaintiffs' proffered experts — Anna Lembke, Katherine Keyes, and Jonathan Gruber — that purport to establish a causal connection between the use of prescription opioids (including their medical use pursuant to a legitimate prescription) and the abuse of illicit opioids including heroin and fentanyl. Plaintiffs' opposition relies on a number of studies in the medical literature, but none supports their experts' extreme position: that prescription opioid use has *caused* illicit heroin and fentanyl abuse today. Plaintiffs seek to use this unsound theory, the “gateway” hypothesis, to recover damages related to the abuse of illicit opioids that no Defendant ever sold, such as damages related to the treatment of individuals who abused heroin. Because there is no support for this speculative and unreliable hypothesis, however, Plaintiffs' proffered experts may not present it to the jury.

### **ARGUMENT**

Plaintiffs suggest that whether there is a causal relationship between prior medical use of prescription opioids and heroin or fentanyl use is an appropriate subject for a “battle of the experts” to be refereed by a jury. Pls.' Mem. in Opp. to Defs' Mot. to Exclude “Gateway” Opinions of Drs. Lembke, Gruber, and Keyes (“Opp.”) at 19 (Dkt. 2197). It is not. That Plaintiffs' experts analyze the available data to reach a conclusion that goes well beyond that of the other scientists on whose work they rely — and do so in a setting that lacks the disciplining scrutiny of peer review — is a key indicator that Plaintiffs' experts have not reliably applied the methodologies they purport to use. *See* Fed. R. Evid. 702(d) & Advisory Committee Notes (“Under the amendment [to Rule 702], as under *Daubert*, when an expert purports to apply principles and methods in accordance with professional standards, and yet reaches a conclusion that other experts in the field would not reach, the trial court may fairly suspect that the principles and methods have not been faithfully applied.”).

**I. In Its Role as *Daubert* Gatekeeper, the Court Should Evaluate Whether the Experts' Conclusions are Inconsistent with the Conclusions of the Studies Upon Which the Experts Rely.**

Plaintiffs wrongly believe this Court is not “permit[ted] . . . to subject an expert’s conclusions, as opposed to his methodology, to the *Daubert* analysis.” Opp. at 3. But the Supreme Court expressly rejected such a bright-line distinction in *General Electric Co. v. Joiner*, 522 U.S. 136 (1997), holding that “conclusions and methodology are not entirely distinct from one another.” *Id.* at 146. Even when an expert purports to use an accepted methodology, the expert must reliably apply that methodology to the underlying data relevant to the issue. *Id.* at 146-47. “[N]ot every opinion reached” by a particular methodology “will meet the standard of reliability required by *Daubert*,” even if that methodology might sometimes produce reliable opinions. *Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 675 (6th Cir. 2010) (quoting *Best v. Lowe's Home Ctrs., Inc.*, 563 F.3d 171, 175 (6th Cir. 2009)).

Accordingly, “nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence which is connected to existing data only by the *ipse dixit* of the expert,” and “[a] court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.” *Joiner*, 522 U.S. at 146; *see also Nelson v. Tenn. Gas Pipeline Co.*, 243 F.3d 244, 254 (6th Cir. 2001); *Davis v. McKesson Corp.*, No. CV-18-1157-PHX-DGC, 2019 WL 3532179, at \*25 (D. Ariz. Aug. 2, 2019) ([A]n expert’s *ipse dixit* cannot be used to connect existing data to an unproven conclusion.”). Specifically, a “trial court . . . may exclude expert testimony based on epidemiological studies where the studies are insufficient, whether considered individually or collectively, to support the expert’s causation opinion.” *Baker v. Chevron USA, Inc.*, 680 F. Supp. 2d 865, 875 (S.D. Ohio 2010).

As the Federal Judicial Center’s Reference Manual on Scientific Evidence notes, epidemiology studies showing a mere association between two variables are alone insufficient to

draw a conclusion of a causal relationship. See REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, 3D ED., 2011 at 598 (Dkt. 2197-12). Rather, researchers must “consider how guidelines for inferring causation from an association apply to the available evidence.”<sup>1</sup> *Id.* The conclusions of the authors of the primary literature on which experts rely are crucial indicia of reliability.

Plaintiffs wrongly suggest the Fifth Circuit’s decision in *Huss v. Gayden* is an outlier because the court required expert causal conclusions to match those of the scientific literature. See Opp. at 6 n.9. In fact, consistent with *Huss*, numerous courts have cited *Joiner* and excluded experts who reached conclusions that were unsupported by the studies upon which the experts relied. See, e.g., *McClain v. Metabolife Int’l*, 401 F. 3d 1233, 1248 (11th Cir. 2005) (excluding expert who drew “unauthorized conclusions from limited data – conclusions the authors of the study do not make”); *In re Accutane Prods. Liab. Litig.*, No. 8:04-md-2523-T-30TBM, 2009 WL 2496444, at \*2 (M.D. Fla. Aug. 11, 2009) (“[W]hen an expert relies on the studies of others, he must not exceed the limitations the authors themselves place on the study.”); *In re Mirena IUS No. II*, 341 F. Supp. 3d at 241 (same); *Davis*, 2019 WL 3532179, at \*17 (excluding experts who cited studies without “acknowledging that the studies’ results or the authors’ conclusions are inconsistent with the experts’ opinions”); *Carnegie Mellon Univ. v. Hoffman-LaRoche, Inc.*, 55 F. Supp. 2d 1024, 1039-40 (N.D. Cal. 1999) (excluding expert who “analyzed data that was not his own and reinterpreted it in a manner inconsistent with the conclusions of those who originally generated it”); *Anderson v. Bristol Myers Squibb*, No. CIV. A. H-95-0003, 1998 WL

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<sup>1</sup> The manual highlights nine separate factors, called the “Bradford Hill factors,” that are commonly considered in drawing a conclusion of causation, see *id.* at 599-600, but even those factors are subject to manipulation unless scientifically weighed and applied. See *In re Mirena IUS Levonorgestrel-related Prods. Liab. Litig. (No. II)*, 341 F. Supp. 3d 213, 268-69 (S.D.N.Y. 2018). Although Plaintiffs now argue in a footnote that the Bradford Hill factors are satisfied, Opp. at 12 n.36, the experts themselves did not conduct this or any other systematic analysis in determining causation. The Court should therefore disregard this last-ditch analysis.

35178199, at \*11-12 (S.D. Tex. Apr. 20, 1998) (excluding expert who drew a “causation conclusion that the authors of the study never even reached in their published work”); *Jones v. U.S.*, 933 F. Supp. 894, 898 (N.D. Cal. 1996) (excluding experts who “claimed that their opinions were supported by numerous scientific articles, [however] a careful reading of these articles reveals that many of their authors came to different conclusions than Plaintiffs’ witnesses did”).

Here too it the Court in its gatekeeper role must scrutinize the methodologies the experts employed to reach a conclusion that use of prescription opioids, and particularly medical use, causes heroin and fentanyl abuse. That Dr. Keyes and Dr. Lembke, in particular, purport to draw causal conclusions from a body of scientific literature that does not support causation, without any reliable or even articulated method for drawing those conclusions, demonstrates that they have applied a methodology that does not meet the *Daubert* standard. And to the extent Dr. Gruber relies on his own quantitative analyses in addition to the epidemiology studies he cites to reach the conclusion that prescription opioid use causes heroin use, Defendants’ Motion to Exclude the Opinions Offered by Dr. Jonathan Gruber, dkt. 1765, addresses why those analyses are inadmissible.

## **II. The Scientific Literature Cited by Plaintiffs and their Experts Does Not Support a Methodologically Reliable Finding of Causation**

Rather than address the deficiencies in their experts’ methodologies, Plaintiffs merely cite a barrage of studies. Many have nothing to do with the issue at hand, none support the experts’ gateway hypothesis, and some were not even materials they considered. This is not acceptable under *Daubert*, nor is it scientifically sound.

Defendants recognize that some users of prescription opioid medications subsequently abuse those medications, other prescription medications, or illicit street drugs like heroin. That

some subset of patients who abused prescription opioids later try heroin is not surprising or revealing. The testimony by federal officials that Plaintiffs cite, *see* Opp. at 15-16, adds nothing more. Indeed, Plaintiffs' experts do not even rely on this testimony, so it cannot support the reliability of their methodologies under *Daubert*. But the question for purposes of this litigation is whether the use of prescription opioid medications *causes* heroin use. Without a causal relationship, it would be improper for a jury to hold Defendants liable for an epidemic of illicit drug addiction — yet, that is exactly what these experts' testimony would invite a jury to do.

As discussed, epidemiological studies showing an association are not sufficient to prove causation. Plaintiffs bristle at the implications of their experts' reliance on observational studies, not controlled clinical trials. But it is a simple fact that observational studies introduce much more uncertainty into an assessment of potential causal relationships. And as set forth in Defendants' opening brief, even the observational studies cited by Plaintiffs do not support the conclusion that a causal relationship exists between prior prescription opioid use, particularly *medical* prescription opioid use, and heroin or illicit fentanyl use.

Plaintiffs instead try to focus the Court's attention on a proposition that Defendants have not challenged pursuant to *Daubert* (although Defendants' experts disagree substantively with Plaintiffs' experts): whether medical use of prescription opioids causes *nonmedical use* of prescription opioids. Most of the studies cited in the opposition address only this alleged relationship and do not involve heroin use at all. *See* McCabe (2011) (Dkt. 2197-8); McCabe (2017) (Dkt. 2197-9); McCabe (2019) (Dkt. 2197-6); Boscarino (2015) (Dkt. 2197-13); Edlund (2014) (Dkt. 2197-10). In some cases, the articles make a passing reference to heroin — Ali (2019) (Dkt. 2197-15); Brummet (2017) (Dkt. 2197-17); and Delgado (2018) (Dkt. 2197-18) — but include no actual data relevant to the experts' hypothesis.

Importantly, *not a single one* of the studies cited by Plaintiffs concludes that prescription opioid use or abuse *causes* heroin use. In fact, in one instance, the author published a supplemental clarification (not cited by Plaintiffs) that specifically *disavowed* a reader's misinterpretation of the study as evidence of causation. Siegal (2003) ("We fear that Dr. Gunderson may have misinterpreted our observations as causal statements. . . . The purpose of our Letter to the Editor was not to attribute increases in heroin abuse to OxyContin specifically, or any other proprietary-name analgesic . . .").<sup>2</sup>

Plaintiffs also point to a report by the National Academies of Sciences, Engineering, and Medicine ("NASEM Report") cited by Dr. Lembke as evidence for the gateway hypothesis. Unlike the experts, however, the NASEM Report acknowledges the continued uncertainty about any potential relationship between prescription opioid use and heroin. In fact, the NASEM Report observes "that an overwhelming majority of people who use prescription opioids do not continue to use them chronically, and so are not at risk of switching to using heroin." Dkt. 2197-1 at 210 (internal citation omitted). The Report also examines the numerous social and cultural factors related to the choice of substances of abuse in particular areas. *See id.* at 210-12. It simply does not provide a reliable scientific basis to opine that there is a causal link between prescription opioid use and illegal opioid abuse.

Similarly, Dr. Keyes's own work as an independent scientist, cited by Plaintiffs as evidence that she has not changed her views due to her work as a paid expert, in fact shows a marked difference in her litigation and non-litigation opinions. Dr. Keyes's 2014 article

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<sup>2</sup> Ex. 1, Letter from Harvey A. Siegal, Am Fam Physician. 2003 Dec 1;68(11):2134, *published in reply to* Letter from Erik W. Gunderson, No data to show link between opioid abuse and heroin use. Am Fam Physician. 2003 Dec 1;68(11):2134.

specifically studied *nonmedical* prescription opioid use. Dkt. 2197-28. The article highlighted that the risk factors for nonmedical prescription opioid use and other illicit drug use are largely similar, and “there is growing evidence that the abuse of other prescription drugs such as stimulants and benzodiazepines is also increasing.” *Id.* at e53, e55. Although Dr. Keyes drew an association between increased medical use of prescription opioids and “increased access to opioids for nonmedical use,” she also recognized that “the large majority of adults who use opioids nonmedically obtain them from friends and relatives or from street level dealers,” and that a “substantial proportion of overdose deaths and emergency department visits occurs among individuals who have never received a prescription.” *Id.* at e53. Finally, she suggested only that the “nonmedical prescription opioid use epidemic *may* portend future increases in illicit drug use as well, considering that nonmedical prescription opioid users are more likely than are nonusers to transition to heroin and other illicit drugs.” *Id.* (emphasis added). Nowhere in this pre-litigation publication did Dr. Keyes draw the unfounded conclusions that she now offers as an advocate: that prior prescription opioid use *causes* current use of heroin and other illicit drugs. Certainly she does not go so far as to argue that 80% of fentanyl deaths are “attributable to prescription opioid use” simply because 80% of heroin users report that they abused prescription opioids prior to starting heroin. Keyes Rpt at 27 (Dkt 2000-9 / 1999-9).

\* \* \*

The vast majority of patients for whom prescription opioid medications are prescribed take them exactly as prescribed by their physician. And even of those individuals who “misuse” prescription opioids (mostly to obtain additional pain relief), only a tiny fraction try heroin – and the vast majority of those previously abused some other illicit substance. It is therefore unsurprising that scientists outside the context of this litigation have not concluded that there is a



causal relationship between prescription opioid medication use and heroin abuse. Plaintiffs' experts, while purporting to review the scientific literature in a reliable fashion, have instead drawn conclusions that are unreliable, unsupported by the available data, and unscientific. If allowed, their speculative conclusions would result in a skewed and prejudicial presentation of evidence to the jury, focused on the harms caused to Ohioans by criminal drug abuse, not Defendants. The Court should accordingly grant Defendants' *Daubert* motion and exclude the opinions of Drs. Lembke, Keyes, and Gruber regarding the gateway hypothesis.

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Respectfully submitted,

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<sup>3</sup> Teva Pharmaceutical Industries Ltd., Allergan plc, and Mallinckrodt plc are respectively an Israeli corporation, Irish holding company, and an Irish company that are not subject to and contest personal jurisdiction for the reasons explained in their motions to dismiss for lack of personal jurisdiction; they are specially appearing to join this motion and, thus, they do not waive and expressly preserve their pending personal jurisdiction challenges.

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**CERTIFICATE OF SERVICE**

I, Geoffrey E. Hobart, hereby certify that the foregoing document was served via  
the Court's ECF system to all counsel of record.

/s/ Geoffrey E. Hobart

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